IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:	)	Group Art Unit: 1651
Starling	)	Confirmation No: 9225
Serial No.: 10/030,578	)	Examiner: DAVIS, Ruth A.
Filed: April 29, 2002	)	**DECLARATION OF KEYVAN BEHNAM UNDER 37 CFR § 1.132**
Atty. File No.: 4141-2-PUS	)	
For: "CALCIUM-CONTAINING STRUCTURES AND METHODS OF MAKING AND USING THE SAME"	)	***Submitted via EFS-web***

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Keyvan Behnam declare as follows:

1. I am a skilled artisan in the field of bone grafts and am familiar with the above referenced application.

2. This Declaration under 37 CFR §1.132 is being submitted in conjunction with a Response to an Office Action mailed on April 27, 2010, the Amendment and Response being filed herewith.

3. This Declaration provides evidence that a skilled person reviewing the disclosure of Radin (CA 2253649) would understand the disclosure of a coating of a biologically active molecule to refer to an amount significantly less than 5% by volume.

4. In Radin cited by the Examiner, it is understood that the use of biologically active molecules described is for coating hollow particles. Radin does not describe an explicit quantity of such biologically active molecules. The only quantitative example of the incorporation of a biologically active molecule given in Radin is found on column 6, line 15. Radin proposes the

use of 1.2 mg of the antibiotic vancomycin per gram of silica; that amounts to a biologically active coating concentration of 0.12%.

5. As described by the references listed below, when biologically active molecules as used in Radin (page 8 lines 9-15: growth factors, cytokines, antibiotics, anti-inflammatory agents, analgesics and cell attachment molecules) are used as a coating, they are present in amounts significantly less than 5%.

A. **Ohyama T, et al., 2004.** β-Tricalcium Phosphate Combined With Recombinant Human Bone Morphogenic Protein-2: A Substitute for Autograft, Used for Packing Interbody Fusion Cages in the Canine Lumbar Spine. *Neurol Med Chir* (Tokyo) 44,: 234-241.

This reference provides an example wherein a growth factor is used as a coating. In this reference the use of 200 micrograms of human bone morphogenic protein-2 (BMP-2), a growth factor, is combined with 3 grams of tricalcium phosphate in a canine fusion model. This results in a biologically active coating concentration of 0.0067%. (see Study Design pgs. 235-236)

B. **Wernike E, et al., 2010.** VEFG Incoporated Into Calcium Phosphate Ceramics Promotes Vascularisation and Bone Formation *In Vivo. European Cells and Materials* 19:30-40.

This reference provides an example wherein a cytokine is used as a coating. In this reference the use of Vascular Enothelial Growth Factor (VEGF) with ceramic disks is described. The authors combine 12.5 micrograms of VEGF (2.5 ml of at 5 microgram/ml VEGF) with 75% porous ceramic disk having a volume of 0.077 ml (diameter of 14 mm and a thickness of 0.5 mm). Estimating the density of the ceramic at 3.15 g/ml the ceramic weight would be 60.6 mg (0.077 ml x 0.25 x 3.15 g/ml). This results in a biologically active coating concentration of 0.02%. (see Materials and Methods section, p. 31)

C. **Mi Woo, K, et al., 2007.** Suppression of Apoptosis by Enhanced Protein Adsorption on Polymer/hydroxyapatite Composite Scaffolds. *Biomaterials* 28(16): 2622-2630.

This reference provides support that bioactive extracellular matrix (ECM) molecules would generally be used at less than 5%. On page 14, Figure 4A shows that the authors add

approximately 3 micrograms of fibronectin or vitronectin to foam disks comprised of hydroxyapatite and polylactic acid (1:1 ratio by weight). The disks are stated to be 8 mm in diameter and 1.5 mm in thickness. That translates to a volume of 0.075 ml. Because the density of hydroxyapatite is 3.156 g/cc and the density of poly(l-lactic acid) PLLA is 1.25 g/cc, we expect the scaffold to contain 28.4% hydroxyapatite by volume. The porosity of the scaffold, however, is stated to be 89.2% in the second paragraph of page 3. That implies a total hydroxyapatite volume of 0.00217 ml (0.075 ml x 0.284 x .108). Multiplying by the density of hydroxyapatite, we get a total hydroxyapatite content of 0.00686 g or 6860 micrograms. That amounts to a fibronectin or vitronectin percentage of 0.043%.

6. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

9/14/10
Date

Keyvan Behnam